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**14. ABSTRACT:**
Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Suspected causes for these health complaints continue to be investigated and include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. Many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. It is the goal of this study to further evaluate the role of pesticides in the development of symptoms reported by GW veterans. This will be accomplished by performing neuropsychological assessments with a group of military pesticide applicators. It is hypothesized that pesticide applicators with high exposures will perform significantly worse on cognitive and neurological measures than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides) will prove to be synergistic and/or additive in terms of decreased cognitive and neurological functioning and increased physical symptoms.

**15. SUBJECT TERMS**
Neurotoxicant Exposures, Neuropsychological Deficits, Gulf War Veterans, Central Nervous System, Pesticides, Pyridostigmine Bromide.

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## INTRODUCTION

Gulf War (GW) veterans continue to complain of short-term memory and mood problems many years following their return from the Persian Gulf. Research to date suggests that it is unlikely that there is one single cause for GW illness but rather suggests that multiple causes in different groups of veterans is the likely the cause of continued health symptoms. Suspected causes for GW veterans continued health complaints include additive and/or synergystic effects of the varying combinations of exposures to pesticides, pyridostigmine bromide (PB), low-level nerve agents, and psychological trauma. Research evaluating the effects of pyridostigmine bromide (PB) exposure on neuropsychological functioning in GW veterans, found significantly lower performance on tasks assessing executive system functioning in the PB exposed GW veterans compared with controls (Sullivan et al., 2003). Pesticide exposure has been associated with mood decrements and residual effects many years after exposure in a large longitudinal cohort of GW veterans (White et al., 2001). In addition, low-level nerve agent exposure (from Khamisiyah weapons arsenal) has been associated with mood complaints and executive system decrements in GW veterans (White et al., 2001).

It has been documented that many pesticides are neurotoxicants as are PB and nerve agents. Two subsets of these chemicals, organophosphates (OP) and carbamates, are known to produce chronic neurological symptoms at sufficient exposure levels. For example, studies of agricultural workers and professional pesticide applicators have found lasting deficits in neurological and cognitive functioning resulting in decreased processing speed and mood complaints (Stephens et al., 1995; Steenland et al., 1994).

It is the goal of this study to further evaluate the role of pesticides in the development of CNS symptoms reported by GW veterans and to assess the additive and/or synergistic effects of combinations of chemical exposures and stress. This will be accomplished by assessing a group of military pesticide applicators with known chemical exposures. It is hypothesized that applicators with high exposures will perform significantly worse on specific cognitive and neurological measures and report more health symptom complaints than a group of GW military personnel with very little pesticide exposure. It is also hypothesized that multiple chemical exposures (PB, pesticides, low-level nerve agents) will be synergistic and/or additive in terms of decreased cognitive and neurological functioning.

The specific aims of this study are: (1) To determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans (2) To determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans (3) To assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

## Body

The approved statement of work for the entire study period is below:

STATEMENT OF WORK

Neuropsychological Functioning in Gulf War Veterans Exposed to Pesticides and Pyridostigmine Bromide.

**Task 1. Develop Plan for Subject Recruitment Months 1-6:**

a. Locate and obtain previous exposure interviews from a group of Gulf War veteran pest-control interviewees (PCI) previously contacted by Office of the Special Assistant to the Under Secretary of Defense for GW illnesses (OSA) in 1997-1998 (months 1-3).
b. SRBI, an independent contracting company (with an 80% success rate) will contact all PCIs and obtain current address and administer a brief follow-up questionnaire (months 3-4).
c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure (months 3-5).
d. Identify pool of potential subjects for each of four exposure categories to recruit (months 4-5).
e. Screen potential subjects for exclusion criteria (months 5-6).

**Task 2. Perform Subject Recruitment and Data Collection Months 6-42:**

a. Study coordinator will contact potential subjects for recruitment and arrange for travel to multiple study sites (months 6-42).
b. Perform cognitive evaluations and psychodiagnostic interviews from 160 study participants (months 6-42).
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for all study subjects (months 6-42).

**Task 3. Data Collection and Interim Analyses, Months 18-42:**

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing (months 18-42).
b. Interim Statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically (months 18-42).
c. Exposure assessment analyses for pesticides and PB will be ongoing (months 18-42).
d. Annual reports of progress will be written (12-36).

**Task 4. Final Analysis and Report Writing, Months 42-48:**

a. Analyze subject characteristics of individuals who were lost to follow-up (months 42-44).
b. Write final study report and prepare manuscripts for submission (months 44-48).

The statement of work for years 1 and 2 is below. The statement of work for year 1 primarily describes the completion of the start-up phase of the study including obtaining the study sample from a group of pest control interviewees (PCIs) previously interviewed by the Deployment Health Support Directorate (DHSD), to obtain current contact information for the PCIs and administer a brief follow-up questionnaire with these individuals. In addition, in year 2, the plan was to recruit 58 additional study participants (50 for year 2 goal plus 8 from previous year's goal) for the study protocol including cognitive evaluations, psychological interviews and exposure questionnaires and perform data entry and cleaning, and preliminary analyses of the data.

Statement of work for Years 1 and 2:

Task 1. Develop a Plan for Subject Recruitment (as stated above):

a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly the OSA) conducted in 1997-1998.
b. Contract with an outside survey company, SRBI, to contact PCIs and obtain current address and administer a brief follow-up questionnaire.
c. Categorize PCIs into high and low exposure groups based on the telephone surveys.
d. Identify pool of potential subjects for each of four exposure categories to recruit.
e. Screen potential subjects for exclusion criteria.

Task 2. Perform Subject Recruitment and Data Collection (specific to year 2):

a. Recruitment of 58 additional study subjects and arrange for travel to multiple study sites
b. Perform cognitive evaluations and psychodiagnostic interviews with 58 additional study participants
c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 58 additional study subjects by study questionnaires.

Task 3. Data Collection and Interim Analyses

a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing
b. Interim statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically.
c. Exposure assessment analyses for pesticides and PB will be ongoing.
d. Annual reports of progress will be written.

**Task 1a. Locate and obtain records of PCI surveys from the Deployment Health Support Directorate (formerly OSAGWI) conducted in 1997-1998.**

The Pesticides Environmental Exposure Report (www.gulflink.osd.mil) commissioned by the Deployment Health Support Directorate provided estimates of exposure for general deployed military and separately for pesticide applicators from the Gulf War based on interviews with the current study sample of pesticide applicators and preventive medicine specialists and a review of DOD pesticide records.

The term "pest control interviewee" (PCI) refers to any of the 298 personnel interviewed by the Office of the Special Assistant for Gulf War Illnesses (OSAGWI) in the course of the "preventive medicine" (PM), "delousing," and other interviews described in OSAGWI's Pesticides Environmental Exposure Report. OSAGWI chose to interview these individuals because it was believed that they would be the most likely to have knowledge of pesticide products used in the Army, Navy, Air Force, and Marines. They were identified based on military occupational specialty (MOS) codes. PCIs include physicians, entomologists, environmental science officers, preventive medicine specialists, field sanitation team members, military police, and other pest controllers. OSAGWI has since been renamed the Deployment Health Support Directorate (DHSD).

The current study is an examination of the CNS effects of neurotoxicant exposure in pest control interviewees (PCI) with known neurotoxicant exposures as a result of their tour of duty at the time of the Gulf War. PCI's comprise specific groups of GW veterans likely to fall into high and low categories of pesticide exposure based on their military occupational specialty (MOS). Each potential participant previously completed a pesticide interview that included self-report measures of exposures to neurotoxicants while in the Gulf region. PCI contact information and interview data (conducted in 1997-1998) were provided to the Principal Investigator by Dr. Michael Kilpatrick, M.D., Deputy Director of the Deployment Health Support Directorate (previously known as OSAGWI) through their System of Records Notice which permits release of records to the Veterans Administration. The DHSD released the records to the VA Boston Healthcare System through a Memorandum of Understanding (MOU). The MOU provided assurances from the VA Boston Healthcare System and the Boston Environmental Hazards Center (a joint program of the VA Boston Healthcare System and Boston University).

| |
|---|
| The MOU states:<br>1) The released PCI records will only be used for the purposes of the current study<br>2) Only study personnel will have access to the released records<br>3) The released information will be safeguard to preserve the confidentiality of the data<br>4) Any personal identifiers will be removed from any interim and final reports that are prepared as a consequence of this study. |

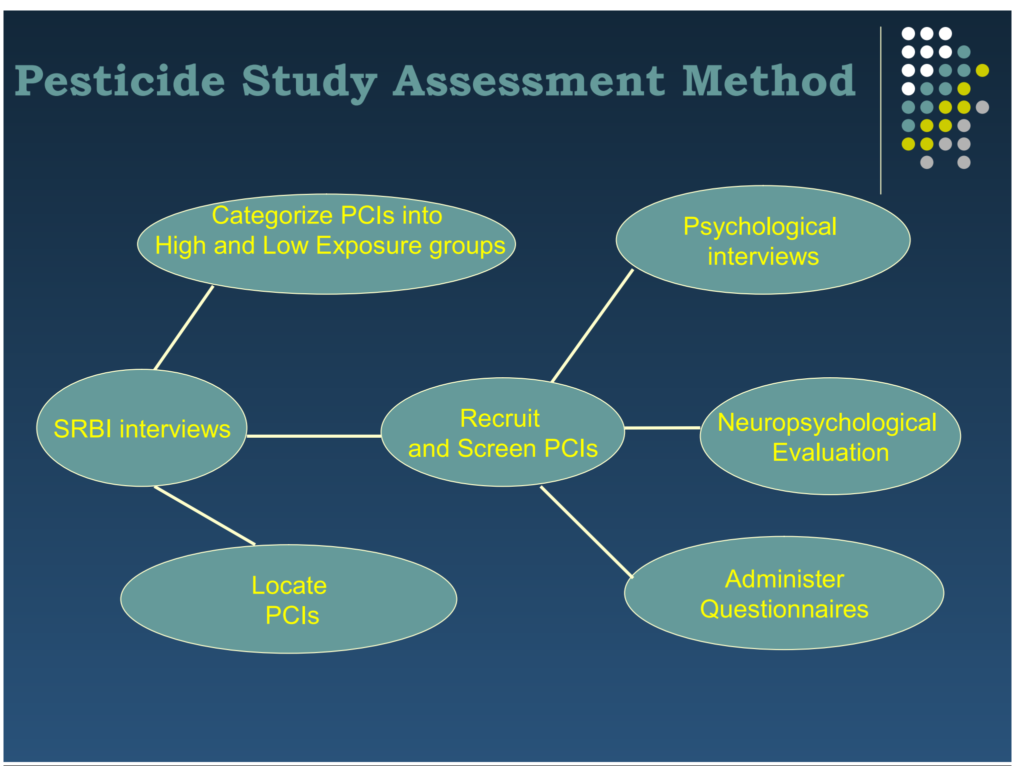
The PCI interview records were used in conjunction with current interview data to categorize individuals into high and low pesticide and PB (pyridostigmine bromide) exposure categories. In addition, these interviews will also be used in conjunction with the current exposure questionnaires to perform dose-estimates for pesticides and PB. Mr. William Bradford, lead author of the Pesticides Environmental Exposure Report, will be available to assist with these dose-estimates in years 2-4.

**Task 1 b. SRBI, an independent contracting company will contact PCIs and obtain current address and administer a brief follow-up questionnaire.**

An outside research firm (Schulman, Ronca, & Bucuvalas, Inc., SRBI) with extensive experience collecting data from veterans of the U.S. Armed Forces was subcontracted to obtain current telephone numbers and addresses for the PCIs and to administer a brief follow-up questionnaire by telephone. The recruitment process was as follows: PCIs were sent a letter from the PI explaining that SRBI would be contacting them to conduct a brief telephone interview and obtain their current contact information for the study. A postage paid opt-out postcard was included with this introduction letter. If the PCI elected to return this postcard, there was no further contact with this individual for the study. If a postcard was not returned to the study staff, SRBI attempted to contact the PCI and determine if they wished to participate in the brief interview regarding their pesticide and PB exposures during the Gulf War. Ten individuals returned the opt-out postcards and were not contacted further for this study. From the remaining list, SRBI was successful in completing 160 telephone interviews with PCIs regarding neurotoxicant exposures resulting in a live refusal rate of just seven percent. SRBI was also able to find current contact information for all 293 PCIs and identify that one PCI was deceased.

The study design is presented in the figure below followed by tables of demographic information computed from the SRBI telephone interview data.

Figure 1. Pesticide Study Assessment Design



From the SRBI telephone interviews, demographic and exposure data was collected from each responding PCI. The demographic information is reported in table 1. From this group of 160 study respondents, 140 were male and 20 were female. The average age for the group of Gulf War veterans was 48 years old and the group was largely Caucasian (85%). The most commonly reported current health problems reported by these study participants were hypertension, cardiovascular disease, arthritis, asthma, back and joint pain, skin rash and memory problems. When broken down into groups based on high and low groups for pesticides and PB, the only notable differences were found in increased reporting of hypertension (12 vs. 6 PCIs), cardiovascular disease (6 vs. 2 PCIs) and arthritis (6 vs. 1 PCI) in the high pesticide group compared with the low pesticide group. While the high and low PB groups did not appear to differ very much with respect to health symptom reporting from this brief health query included in the telephone interviews. The larger study questionnaire with more in-depth questions regarding medical diagnoses will help to better characterize these groups in terms of health outcomes and show their significance. The demographic breakdown of the SRBI surveys is reported in table 1.

Table 1. Demographic Breakdown for SRBI Survey Respondents

| Gender | Frequency | Percent |
|---|---|---|
| Male | 140 | 87.5 |
| Female | 20 | 12.5 |
| Total | 160 | 100 |

Current Age for SRBI Survey Respondents

| Minimum | Maximum | Mean |
|---|---|---|
| 33 | 74 | 47.7 |

Ethnicity for SRBI Survey Respondents

| Ethnicity | Frequency | Percent |
|---|---|---|
| African American | 12 | 7.5 |
| Asian American | 3 | 1.9 |
| Caucasian | 136 | 85.0 |
| Hispanic American | 6 | 3.8 |
| Other | 3 | 1.9 |

Health Symptom Self-report for SRBI Respondents

| Symptom | Frequency | Percent |
|---|---|---|
| Hypertension | 23 | 14 |
| Cardiovascular Disease | 11 | 7 |
| Arthritis | 12 | 8 |
| Asthma | 10 | 6 |
| Back Pain | 11 | 7 |
| Joint Pain | 13 | 8 |
| Skin Rash | 14 | 9 |
| Memory Problems | 14 | 9 |

**Task 1 c. Categorize PCIs into high and low exposure groups for pesticides and pyridostigmine bromide (PB) exposure.**

Pesticides were used widely in the Gulf War to protect troops from such pests as sand flies, mosquitoes and fleas that can carry the infectious diseases leishmaniasis, sand fly fever and malaria. Indeed, of the nearly 700,000 US troops deployed to the Gulf region, only 40 cases of infectious diseases were documented (Winkenwerder Jr, W., 2003). US forces used pesticides in areas where they worked, slept, and ate throughout the GW. In fact, on any given day during their deployment, GW veterans could have been exposed to 15 pesticide products with 12 different active ingredients and pesticide applicators were likely exposed to more pesticide products and at higher doses. Troops used pesticides for a number of reasons, including personal use on the skin and uniforms as an insect repellent, as area sprays and fogs to kill flying insects, in pest strips and fly baits to attract and kill flying insects, and as delousing agents applied to enemy prisoners of war. These widespread, commonly reported uses supported the decision by the OSAGWI to investigate pesticide exposures as a potential contributor to unexplained illnesses in GW veterans. According to the OSAGWI report, the pesticides of potential concern (POPCs) used by US military personnel during the GW can be divided into five major classes or categories:
1) organophosphorus pesticides, such as malathion and chlorpyrifos; 2) carbamate pesticides, such as bendiocarb; 3) the organochlorine, lindane; 4) pyrethroid pesticides, such as permethrin; and 5) the insect repellent DEET (see figures 2 through 4).

**Figure 2. Pesticide use and Application Overview.**

## Pesticide Use and Application Overview

| Use | Designation | Purpose | POPCs, Active Ingredient | Application Method | User or Applicator |
|---|---|---|---|---|---|
| General Use Pesticides | Repellents | Repel flies and mosquitoes | DEET 33% cream/stick | By hand to skin | Individuals |
| | | | DEET 75% Liquid | By hand to skin, uniforms or netting | |
| | | | Permethrin 0.5% (P) Spray | Sprayed on uniforms | |
| | Area Spray | Knock down spray, kill files and mosquitoes | d-Phenothrin 0.2% (P) Aerosol | Sprayed in area | |
| | Fly Baits | Attract and kill flies | Methomyl 1% (C) Crystals | Placed in pans outside of latrines, sleeping tents | Individuals, Field Sanitation Teams, Certified Applicators |
| | | | Azamethiphos 1% (OP) Crystals | | |
| | Pest Strip | Attract and kill mosquitoes | Dichlorvos 20% (OP) Pest Strip | Hung in sleeping tents, working areas, dumpsters | |
| Field Use Pesticides | Sprayed Liquids (emulsifiable concentrates, ECs) | Kill flies, mosquitoes, crawling insects | Chlorpyrifos 45% (OP) Liquid | Sprayed in corners, cracks, crevices | Field Sanitation Teams or Certified Applicators |
| | | | Diazinon 48% (OP) Liquid | Sprayed in corners, cracks, crevices | Certified Applicators |
| | | | Malathion 57% (OP) Liquid | | |
| | | | Propoxur 14.7% (C) Liquid | | |
| | Sprayed Powder (wettable powder, WP) | Kill flies, mosquitoes, crawling insects | Bendiocarb 76% (C) Solid | | |
| | Fogs (Ultra-Low Volume Fogs, ULVs) | Kill flies, mosquitoes | Chlorpyrifos 19% (OP) Liquid | Large area fogging | Certified Applicators |
| | | | Malathion 91% (OP) Liquid | | |
| Delousing Pesticide | Delousing Pesticide | Kill lice | Lindane 1% (OC) Powder | Dusted on EPWs, also available for personal use | Certified Applicators, Military Police, Medical Personnel |

**Figure 3. Active ingredients in pesticides of potential concern.**

## Active ingredients contained in pesticides of potential concern

| Repellents | Pyrethroids | Organophosphates | Carbamates | Organochlorines |
|---|---|---|---|---|
| DEET | Permethrin | Azamethiphos | Methomyl | Lindane |
| | D-Phenothrin | Chlorpyrifos | Propoxur | |
| | | Diazinon | Bendiocarb | |
| | | Dichlorvos | | |
| | | Malathion | | |

**Figure 4. Applicator exposure levels reaching levels of concern**

## Applicator personnel additional exposures which exceeded the levels of concern

| Pesticide | Active Ingredient/Class | Exposure Scenario |
|---|---|---|
| **Sprayed liquids** | Chlorpyrifos (OP) | High |
| | Diazinon (OP) | Medium, High |
| | Malathion (OP) | High |
| **Sprayed powders** | Bendiocarb (C) | Low, Medium, High |
| **Fogs** | Chlorpyrifos (OP) | High |
| | Malathion (OP) | High |
| **Delousing** | Lindane (OC) | Medium, High |

OP = Organophosphate
C = Carbamate
OC = Organochlorine
*Lindane use also may increase the risk of cancer

Guidelines for pesticide and PB exposure are presented in the tables 2 and 3 and were used to classify participants into high and low exposure categories based on prior OSAGWI interviews and current interviews conducted by SRBI.

**Table 2. Guidelines for Pesticides**

**Low exposure**

An individual is assigned to the low-exposure category for pesticides if he or she does not fit the guidelines for high exposure, as described below. For example, an individual exposed to pyrethroids other than via fogs, but no other pesticides, would be assigned to a low pesticide exposure group.

**High exposure**

An individual is assigned to the high-exposure category for pesticides if any of the following apply:

1) PCI reported experiencing acute signs and/or symptoms of pesticide overexposure, other than minor skin irritation, at least once. A general statement, such as "became ill" will qualify.

2) PCI probably applied pesticides from any of the following groups on two or more occasions: organophosphate (OP) emulsifiable concentrate (EC) or ultra low volume (ULV) products, carbamate ECs or powders, lindane used for enemy prisoners of war (EPWs), fly baits ($\geq$2 pounds handled), and/or fogs. PCI may or may not have worn adequate personal protective equipment (PPE).

3) PCI was probably present during applications of OP ECs/ULVs, carbamate ECs/powders, DDT, and/or fogs on two or more occasions.

4) PCI probably spent at least 1 week living/working in structures treated inside with OP and/or carbamate ECs, ULVs, powders, DDT, and/or pest strips, and likely experienced substantial post-application exposure.

5) PCI probably applied DEET to self at least 30 times. PCI must provide enough information to conclude that usage was equivalent to or above this level. DEET application 30 times per month is the 25$^{th}$ percentile value determined by the RAND (2000) survey for ground forces who used DEET (50% reported no use).

**Table 3. Guidelines for PB**

**Low exposure**

An individual is assigned to the low-exposure category for PB if no acute signs and/or symptoms of exposure were reported *and* any of the following apply:

1) The individual reported not using PB.

2) The total dose reported was less than or equal to 180 mg PB active ingredient.

3) The individual reported using PB, but could not recall sufficient details to conclude that the dose was probably greater than 180 mg PB active ingredient.

**High exposure**

Individuals are assigned to the high-exposure category for PB if either of the following apply:

1) The total dose was probably greater than 180 mg PB active ingredient.

2) The individual reported taking any PB and also reported experiencing acute signs and/or symptoms of exposure.

PB and pesticide exposure were categorized as high and low based on the previous OSAGWI interviews and the current SRBI interviews. From these interviews, 97 PCIs were categorized in the high pesticide exposure group and 63 PCIs were categorized in the low pesticide exposure group and 81 PCIs were categorized in the high PB group and 79 PCIs were categorized in the low PB group. Additional categorization for pesticide and PB exposure and Khamisiyah notification (identifying those potentially exposed to chemical weapons) are listed in table 4.

**Table 4. PB and Pesticide Exposure Categories**

| **Self-reported PB Exposure during the Gulf War** | | |
|---|---|---|
| | **Frequency** | **Percent** |
| **Yes** | **118** | **74** |
| **No** | **33** | **20** |
| **Don't Know** | **9** | **6** |
| **Total** | **160** | **100** |
| **Self-reported Pesticide Exposure during the Gulf War** | | |
| | **Frequency** | **Percent** |
| **Yes** | **122** | **76** |
| **No** | **30** | **19** |
| **Don't Know** | **8** | **5** |
| **Total** | **160** | **100** |
| **Exposure Categories for PB and Pesticides** | | |
| | **PB** | **Pesticides** |
| **Low** | **79** | **63** |
| **High** | **81** | **97** |
| **Total** | **160** | **160** |
| **Khamisiyah Weapons Depot Notification** | | |
| | **Frequency** | **Percent** |
| **Yes** | **59** | **37** |
| **No** | **101** | **63** |
| **Total** | **160** | **100** |

**Task 1 d. Identify pool of potential subjects for each of four exposure categories to recruit.**

Combining the previously described high and low exposure groups for the pesticide and PB groups allowed for four category groupings (table 5). The categories include high pesticide and high PB exposure, high pesticide and low PB, low pesticide and high PB, and low pesticide and low PB. The goal of the study was to recruit 40 study participants from each of the four exposure categories with the study participants sequentially assigned to one of the four study groups based on exposure combination. However, the high pesticide/low PB (n =37) and the low pesticide/high PB (n = 20) groups appear to be smaller than expectation and may not allow for such large groupings (table 5). However, analyses controlling for different exposure groups will be employed to control for different group sizes if necessary.

**Table 5. Four Exposure Categories for PB and Pesticides**

| | Pesticide categories | | |
|---|---|---|---|
| **PB categories** | **Low** | **High** | **Total** |
| **Low** | **42** | **37** | **79** |
| **High** | **20** | **61** | **81** |
| **Total** | **62** | **98** | **160** |

**Task 1 e. Screen potential subjects for exclusion criteria.**

The exclusion criteria for this study include current substance abuse, substantial traumatic brain injury or other documented neurological illness precluding the use of a computer. Prior substance abuse and current medications are recorded but do not constitute exclusion criteria.

These exclusion criteria were chosen so that study participants who may perform poorly on cognitive testing for known reasons other than environmental exposures could be screened out to prevent potential study confounders.

From the SRBI telephone interviews, a review of reported health symptoms was performed and no participant from these interviews reported significant head injury or other significant neurological illness that might interfere with performing the cognitive and computer testing parts of the study protocol. There was one case reported of a brain tumor recently removed and a case of multiple sclerosis (MS). However, the study participant with MS was one of the first recruited study participants for the cognitive evaluations and was able to complete the entire study protocol. In the 10 recruitment trips conducted to date, none of the study participants were screened out.

Subject recruitment is ongoing and PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain a serious brain injury. Screening for exclusion criteria occurs during the telephone recruitment phase of the study and will be ongoing during the study recruitment efforts.

**Task 2a. Recruitment of 58 study subjects and arrange for travel to multiple study sites.**

Forty-seven participants were recruited during year 2 and completed the study protocol (cognitive evaluation, psychological interviews and exposure questionnaires). This group included 42 men and 5 women including 4 active duty personnel and 43 veterans. Combined with the year 1 recruitment total of 12 study participants, a total of 59 study participants have been recruited to date. Subject recruitment efforts are presented in the table below. Seven additional subjects were interested in participating in our study but either had schedule conflicts during our recruitment trip to their area (n = 4), became unexpectedly ill and had to cancel their appointment with us (n = 2) or cancelled for no stated reason (n = 1).

**Table 6. Subject Recruitment Efforts for Year 1 and Year 2**

| **Study Year** | **Frequency** | **Projected** | **Percent** |
|---|---|---|---|
| **Year 1** | **12** | **20** | **60%** |
| **Year 2** | **47** | **50** | **94%** |
| **Total recruitment** | **59** | **70** | **84%** |

During year 2, recruitment trips were conducted in Florida, Texas, Pennsylvania, Virginia, Maryland, New York, Georgia and Tennessee. Although 70 study subjects were originally projected to be recruited for Years 1 and 2, an 84 percent recruitment rate was achieved for total recruitment and only six individuals declined to participate. These recruitment trips were successful with only three cancellations of scheduled participants. Although the current address for each PCI was obtained by SRBI during their telephone interviews, we have found that many of the PCIs are quite mobile and have moved to different states from their previous SRBI interview residence. In addition, five of the active duty personnel have been deployed oversees or activated domestically to aid in hurricane relief and were subsequently not able to participate in the study. The recruitment strategy will continue to target the more populated areas first and the next planned recruitment trips will be to Washington State, North Carolina, South Carolina, Wisconsin, Colorado, Nebraska, Kansas and California. We also plan to use internet and other available telephone searches to obtain current residences for participants who have moved. It is anticipated that the recruitment of 61 additional study participants (50 projected for Year 3 plus 11 from Year 2 projections) will be obtainable by the end of Year 3 for a total of 120 recruited study participants. Given the favorable response from the first two years of recruitment efforts, significant difficulties with subject recruitment are not anticipated at this time although additional smaller recruitment trips will likely be necessary to achieve this recruitment goal for year 3.

The exposure classifications are presented below and include 40 high pesticide, 19 low pesticide, and 31 high PB, 28 low PB categories.

**Table 7. Exposure Classifications for First 59 Study Participants**

| | **Pesticide Categories** | | |
|---|---|---|---|
| **PB categories** | **Low** | **High** | **Total** |
| **Low** | **13** | **15** | **28** |
| **High** | **6** | **25** | **31** |
| **Total** | **19** | **40** | **59** |

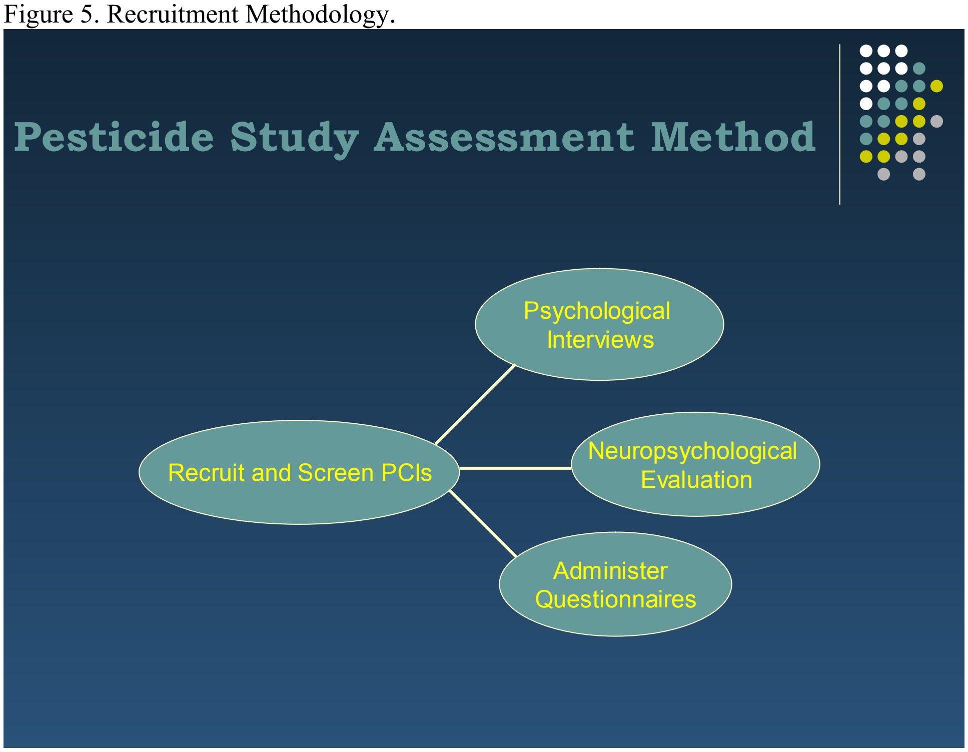
**Table 8. PCI Current Residence by State**

| | | | |
|---|---|---|---|
| AK | 1 | MN | 1 |
| AL | 5 | MO | 23 |
| AR | 6 | MS | 3 |
| AZ | 4 | MT | 2 |
| CA | 9 | NC | 14 |
| CO | 9 | NE | 5 |
| CT | 1 | NJ | 2 |
| DC | 1 | NM | 3 |
| DE | 1 | NY | 8 |
| FL | 24 | OH | 4 |
| GA | 12 | OK | 3 |
| GU | 1 | OR | 1 |
| HI | 4 | PA | 8 |
| IA | 2 | RI | 2 |
| IL | 3 | SC | 6 |
| IN | 1 | TN | 15 |
| KS | 6 | TX | 20 |
| KY | 2 | UT | 2 |
| LA | 2 | VA | 17 |
| MA | 3 | WA | 13 |
| MD | 10 | WI | 9 |
| ME | 1 | WV | 1 |
| MI | 9 | Active duty | 14 |

Recruitment Methodology

When recruiting study participants, the PI or study staff contact PCIs participating in the SRBI interviews to describe the study and establish whether the PCI will participate in the cognitive evaluation. The initial contact with the study staff consists of a description of the study, describing the types of assessment, time required, and reimbursement for their time and effort. Subjects have an opportunity to ask questions about the procedure. They are informed that whether or not they participate will have no bearing on their medical care and that, if they choose to participate, they may withdraw at any time without prejudice. They are asked to indicate whether they wish to participate, wish not to participate, or wish to defer this decision. In the latter case they are asked whether we may contact them again to determine their decision. Gulf War veterans who are currently on active duty are contacted at home in the evening hours and will not be contacted during duty hours. Active duty PCIs are not compensated for their participation as there are restrictions on compensation to active duty personnel. PCIs consenting to participate are asked questions to determine whether they meet preliminary inclusion criteria for the study (that is, that they participated in the OSAGWI interviews (1997-1998), are not currently in treatment for alcohol or other substance abuse, do not have sensory or motor impairments precluding use of the computer, and did not sustain serious brain injury). Prior substance abuse and current medications are recorded but do not constitute exclusion criteria. An appointment during one of the field trips is scheduled for subjects agreeing to participate. PCI veterans retained in the study sample are presented the study consent form for signature. The study methodology is presented in figure 5.

Figure 5. Recruitment Methodology.



**Task 2b. Perform cognitive evaluations and psychodiagnostic interviews with 58 participants**

The goal for year 2 was to recruit and perform cognitive and psychodiagnostic interviews with 58 study participants. As described above, a total of 47 study participants were recruited in year 2 due to residence changes and some scheduling conflicts with potential participants. However, all 47 of the study participants completed the entire study protocol and did not express any difficulties with the length of the examination. The cognitive evaluations were completed in 1.5 hours for most of the study participants and the psychodiagnostic interviews required an additional twenty minutes in most cases to complete. Study participants are able to take breaks during the study protocol session if they feel they need them and can fill out their questionnaires and mail them back if necessary. With this strategy, it is not anticipated that there will be much missing data from the study protocols. However when missing data is encountered during data analysis, interpretative statistics will be employed whenever possible.

A description of the neuropsychological domains and the complete neuropsychological test battery are presented in tables 9 and 10 followed by a description of the study instruments and procedures.

**Table 9. Definitions of Neuropsychological Domains**

| |
|---|
| I. General Intelligence: IQ scores in all domains or in a specific domain (verbal or visual-motor); academic skills; performance on tests of reading, spelling, arithmetic, vocabulary, academic knowledge. |
| II. Attention, Executive System: Capacity to focus on incoming stimuli; includes vigilance, tracking and capacity to divide attention between competing stimuli. |
| III. Motor: Speed and dexterity in completing tasks. |
| IV. Visuospatial function: Processing of nonverbal information such as visual designs, visual constructions, and geographic information; includes sequencing, organization (mental) and constructional ability. |
| V. Memory: Anterograde memory function involves encoding, storing, retrieving and retaining new information. Retrograde memory function refers to ability to recall information learned in the past. |
| VI. Mood/Personality: Includes temporary and characterologic mood states and characterologic personality traits or tendencies. |
| VII. Motivation and Malingering: An evaluation of effort. |

**Table 10. Full Neuropsychological Test Battery.**

| TEST NAME | DESCRIPTION | OUTCOME MEASURE |
|---|---|---|
| **I. Tests of Premorbid Functioning** | | |
| Wechsler Adult Intelligence Scale-Revised (WAIS-III; Wechsler, 1997) Information subtest | Information usually learned in school; to assess native intellectual abilities | Raw Score |
| Boston Naming Test (BNT; Kaplan et al., 1983) | Confrontation naming of line drawings; to assess verbal abilities | Raw Score |
| **II. Tests of Attention, Vigilance and tracking** | | |
| Trail-making Test (Reitan &Wolfson, 1985) | Timed connect-a-dot task to assess attention and motor control requiring sequencing (A) and alternating sequences (B) | Completion |
| Computerized Continuous Performance Test (CPT; Letz & Baker, 1988) | Target letter embedded in series of distractors; to assess sustained attention and reaction time | Reaction Time<br>Total Errors |
| Wisconsin Card Sorting Test (WCST; Heaton et al, 1993) | Requires use of feedback to infer decision making rules; assesses problem solving ability and flexibility | Total # Sorts |
| **III. Tests of Motor Function** | | |
| Finger Tapping Test (FTT; Letz and Baker, 1988) | Speed of tapping with index finger of each hand; assesses simple motor speed | Mean Taps |
| Grooved Pegboard Test (Klove, 1963) | Speed of inserting pegs into slots using each hand separately; assesses motor coordination and speed | Raw Score |
| **IV. Tests of Visuospatial Function** | | |
| Hooper Visual Organization Test (HVOT; Hooper, 1958) | Identifying objects from line drawings of disassembled parts; assesses ability to synthesize visual stimuli | Raw Score |
| Rey-Osterreith Complex Figure (ROCFT; Corwin & Blysma, 1993) | Copying a complex geometric design; assess ability to organize and construct | Raw Score |

| TEST NAME | DESCRIPTION | OUTCOME MEASURE |
|---|---|---|
| **V. Tests of Memory** | | |
| California Verbal Learning Test (CVLT II; Delis et al., 1987) | List of 16 nouns from 4 categories presented over multiple learning trials with recall after interference; assesses memory and learning strategies | Total Trials 1-5<br>Long Delay |
| ROCFT-Immediate and 20 minute recall | Immediate and Delayed recall of a Complex figure | Raw Score |
| Stanford-Binet Copying Test (Terman & Merrill, 1973) | Immediate and 10 minute delay of 16 designs | Raw Score |
| **VI. Tests of Personality and Mood** | | |
| Profile of Mood States (POMS; McNair et al., 1971) | 65 single-word descriptors of affective symptoms endorsed for degree of severity and summed on six mood scales | T-Scores |
| **VII. Tests of Motivation** | | |
| Test of Motivation and Malingering (TOMM; Tombaugh, 1996) | Immediate forced choice recognition of line drawings of 50 common objects; assesses motivation and malingering | Raw Score |

Assessment Instruments and Procedures

1. Cognitive Assessment.

A tester who is blind to the exposure status of the subject administers the neuropsychological test battery. The neuropsychological test battery assesses the functional domains of general intelligence, attention, executive abilities, motor function, visuospatial skills, memory, and mood (table 9). The battery is described in detail in Table 10. It includes 1) tests designed to tap relatively stable native intellectual abilities including the Information subtest from the WAIS-III, and the Boston Naming Test. On these tests, it is expected that the scores will be consistent with estimated native IQ based on age, education, and occupational history and 2) tests shown to have high specificity and sensitivity for detecting changes in neuropsychological functions that have in past studies demonstrated utility in the assessment of toxicant-induced brain damage, and psychiatric disorders. The domains included in this category are attention and executive function, motor skills, mood and memory.

Sustained attention is measured by number of errors on a test of continuous performance (CPT), a computer-assisted test from the Neurobehavioral Evaluation System (NES), an instrument widely used in the field of occupational health, that represent adaptations of traditional neuropsychological instruments for computerized stimulus presentation and recording of responses. The NES instruments have reliable psychometric properties and have demonstrated validity in epidemiological and laboratory studies of exposure to a wide variety of neurotoxicants. Also used as measures of executive functioning, are measures of cognitive flexibility (Wisconsin Card Sort test) and alternation of set (Trail making test, part B).

Motor functioning is measured by the mean of five trials on each hand on the finger tap test, the time to completion on the grooved pegboard test and reaction time on the CPT test.

Previous studies of occupational pesticide exposure have documented changes in reaction time and motor speed (NCTB). Therefore, we predict decreased CPT reaction time performance in the high-exposed PCI group and motor slowing on the additional measures.

The test battery also includes the Profile of Mood states as a self-report assessment of current mood. The indicators of importance are current fatigue, confusion, tension and depression. Mood has been shown to be associated with changes in subcortical-limbic system and neurotransmitters as a result of toxicant exposures and as such, mood will be treated as an outcome measure rather than as strictly a potential confounding variable.

In order to assess visuospatial processing, we will administer the Rey-Osterrieth Complex Figure Test and document total scores for the copying subtest (rey-osterrieth scoring out of 36). We expect that individuals with increased exposures will have difficulty maintaining the overall configuration, tremulous writing and segmentation as a result of basal ganglia dysfunction commonly seen in these people. In addition, the Stanford Binet copying task will be used in this test battery to document further impairment in visuoconstruction as has been found in our prior research. The total score for copying (out of 16 possible) is expected to be diminished in those who have significant neurotoxicant exposures.

Individuals who have documented exposures to neurotoxicants have had difficulty in the areas of acquisition and retrieval. Therefore, we will be examining verbal and nonverbal memory with the use of the Rey-Osterrieth Complex Figure Immediate and Delayed recall and the CVLT-II measures of total recall trials 1 to 5 (raw score) and Long-delay free recall (raw Score).

Lastly, a measure of response consistency will be used to document the possibility of diminishment in motivation. Raw scores (out of a possible score of 50) will be computed and we expect that only a few individuals will fall below a score of 45 (indicating decreased motivation). In the event of decreased motivation scores on this test, analyses will be performed with and without these individual's test scores to assess for potential differences. If there are significant differences between the groups, then the group with low motivational scores will be removed from the dataset.

Because this study compares neuropsychological functioning in pesticide-exposed individuals many years after their GW exposures, the question arises how does one decide if decreased performance in cognitive functioning is actually associated with pesticide exposure or if those individuals with cognitive deficits simply report more pesticide exposure. One way to examine this problem with self-reported exposures and correlating them with current brain functioning is by comparing <u>patterns</u> of cognitive performance in relation to the reported exposure. The field of behavioral neurotoxicology is an established field that studies the effect of brain/behavior (test performance) relationships and specific types of neurotoxicant exposures.

Epidemiological studies during the past 30 years have examined the impact of exposure to metals (e.g., lead, mercury, arsenic), organic solvents (e.g., trichloroethylene, n-hexane, petroleum distillates), and pesticides (e.g., organophosphates, carbamates) on brain functioning and found different cognitive patterns with these exposures.  For example, studies of solvent exposure have reliably shown disturbances in executive function, attention, visuospatial skills, short-term memory, and mood (Anger, 1990, White et al., 1992 and Echeverria& White, 1992) Studies of lead-exposed workers have yielded similar findings along with decrements in verbal reasoning and motor functions (Baker et al., 1984, Hanninen et al., 1978 and Yokoyama et al., 1988). While studies of pesticide-exposed agricultural workers have shown disturbances in processing speed and mood and sequelae from overt poisoning from organophosphate pesticides can result in lasting deficits in the domains of visuomotor, attention/executive functioning, motor functioning and mood. Therefore, we would be comparing not only specific test performance to self-report of pesticide exposure but also the <u>pattern</u> of cognitive performance in the domains of attention/executive functioning, memory, visuospatial skills, motor skills and mood.

In addition to exposure class, other factors (e.g., age, education, intelligence, prior exposures, medical and health concerns, alcohol abuse, life stress, and workplace stress) are likely to influence performance on cognitive tests (Grasso et al., 1984, Hanninen, 1988, Proctor et al, 1996 and Letz, 1993.) and must be taken into account in evaluating the effects of exposure to known or suspected toxicants. Therefore, the study was designed to be able to compare cognitive patterns on five different domains in individuals reporting higher and lower pesticide exposures (table 9).

We have made specific hypotheses of how the higher pesticide exposed individuals will perform based on prior epidemiological studies showing the cognitive pattern of motor (performance speed) and mood decrements in pesticide exposed individuals. We have also included a series of questionnaires to the study protocol that will obtain demographic (age, education, gender, premorbid intelligence) and diagnostic variables (Post-Traumatic Stress Disorder, Major Depression etc.) that could affect cognitive performance and should be controlled for in any analyses comparing self-reported exposures to neurotoxicants. In addition, an exposure questionnaire is also included in the study protocol (SNAC) that queries for other types of neurotoxicant exposures that could affect cognitive performance (exposures from hobbies and post-military employment) that will also be used as control variables.

2. Psychological Assessment.

1) Subjects are administered the Structured Clinical Interview for DSM-IV (SCID) and a current Global Assessment of Functioning score is assessed. This instrument has demonstrated reliable psychometric properties for determining the presence or absence of current or past major Axis I disorders. Dr. Krengel who will also be blind to the exposure data administers the Clinician Administered PTSD Scale IV (CAPS), a state-of-the-art instrument for confirming the diagnosis of

current or past PTSD and for evaluating the intensity, frequency, and severity of the disorder and its individual symptom criteria. Extensive research now indicates that this instrument has highly acceptable psychometric properties. Subjects fill out a series of self-report, paper and pencil measures designed to confirm and define symptoms of PTSD (PTSD checklist), and to identify traumatic events, military or civilian (Modified Life Events Checklist, Traumatic Events) (table 11).

2) Dr. Krengel also conducts a semi-structured clinical interview eliciting information pertaining to recent past and current mood disorders, substance use, neurological and medical illness, traumatic brain injury, and history of other traumatic events. Subjects are asked questions specifically related to recent occupational history (including possible occupational exposure to neurotoxicants), family history of psychiatric disorder, and life stressors.

## Treatment of Data

The aims of this study are to determine the cognitive and neurological effects of pesticide exposure in specific groups of GW veterans, to determine the cognitive and neurological effects of PB exposure in specific groups of pesticide exposed GW veterans, and to assess for interaction effects in GW veterans with multiple chemical exposures (PB, pesticides, low-level nerve agents).

We will examine the relationship between neurotoxicant exposure and neuropsychological performance through multivariate multiple regression. This will include indicator variables to account for group status (1 = High PB, High Pesticide, 2 = High PB, low Pesticide, 3 = Low Pesticide, High PB, 4 = low Pesticide, Low PB) as well as individual risk factors and intervening risk factors that might be related to outcomes. Additional analyses exploring the interactions between the exposures and neuropsychological outcome will be pursued. We will look at the relationship of stress and health symptoms through the multiple regression analyses as described above. Steps have been employed to minimize missing data including offering breaks during cognitive testing, allowing participants to complete questionnaires at home and mailing them back and completing psychological interviews by telephone (when necessary due to time constraints or fatigue of study participants). However when data is not obtainable, the missing data will be interpolated statistically whenever possible by comparing means of similarly answered questions.

**Task 2c. Obtain information about current health status, environmental and occupational exposures, medical or psychological treatments, and any recent medical or psychiatric diagnoses for 58 study subjects by study questionnaires.**

All forty-seven study participants recruited in year 2 completed the study questionnaire. The study questionnaire is comprised of several health and mental health scales. These include: the health symptom checklist, Brief Symptom Inventory (BSI), PTSD checklist (PCL), Modified Life Events Checklist (Traumatic events), Veterans Version of the SF12 (SF12V), and the pesticide exposure questionnaire (SRBI questionnaire). See Table 11 for questionnaire descriptions and Table 12 for frequencies of psychiatric diagnoses, medical conditions and health symptom reports for the first 59 study participants. In general, psychiatric diagnoses were relatively low for PTSD (7 %) and depression (8%) for the entire recruitment sample. The most common medical diagnoses in the study sample included arthritis, allergies, hypertension and asthma. In depth health symptom questions from the health symptom checklist (HSC) in the study questionnaire showed elevated rates in sleep difficulties (61%), concentrating difficulties (51%), forgetfulness (54%) and joint pain (71%). These same health symptoms were the most commonly reported in our prior studies and clinical evaluations of treatment-seeking Gulf War veterans from the New England area (Sullivan et al., 2003). When comparing health symptoms and medical diagnoses by pesticide exposure, all diagnoses were higher in the high pesticide exposed group, (diabetes 2 vs. 0; heart attack 2 vs. 0; arthritis 13 vs. 8, chronic rash 6 vs. 1; high blood pressure 13 vs. 5) but no significant differences were found. Complete analyses between exposure groups will be done when a larger study sample is recruited and higher statistical power is attained.

**Table 11.** **Study Questionnaire Descriptions**

| **Name** | **Description** |
|---|---|
| Demographics | Subjects report information on age, education, gender, ethnicity, marital status, GW duty service (active vs. reserve/National Guard), military rank and current military status. |
| SF12V | Veterans version of the SF12 which compares functional health-related quality of life. It includes a physical component score and a mental component score. |
| Health Symptom Checklist (HSC) | A comprehensive list of 34 frequently reported health and mental health symptoms. The HSC determines how often in the past 30 days the health symptoms were experienced. Symptoms from nine body systems are assessed (cardiac, pulmonary, dermatological, gastrointestinal, genitourinary, musculoskeletal, neurological, and psychological). |
| Medical Conditions | Included in this checklist is a list of 21 medical conditions that the subject is asked to rate if they have ever had the condition, how it was diagnosed (self or doctor) and when it was diagnosed. |
| Brief Symptom Inventory (BSI) | The Global Severity index of the BSI is a summary index that represents the most sensitive single inventory indicator of a subjects' psychological distress level by combining information on a number of psychological symptoms and their intensity. |
| PTSD checklist (PCL) | A 17-item checklist following DSMIII-R or DSM-IV guidelines and is a structured interview for clinical diagnosis of PTSD. |
| Modified Life events checklist (Traumatic Events) | Modified version of the life events checklist to check for traumatic life events. |
| Structural Neurotoxicant Assessment Checklist ( SNAC) | The SNAC assesses the degree of past exposure to neurotoxicants during civilian and military occupations includes questions pertaining to recent occupational and environmental exposures. Questions include length stay, geographical location, and environmental exposure during deployment (type, intensity, frequency, duration, locale). |
| Pesticide Exposure Questionnaire (SRBI brief questionnaire) | This telephone interview will be conducted by SRBI to obtain pesticide and PB exposure estimates. Questions include what pesticides were used during the Gulf War and what health problems that the respondent currently reports. |
| Telephone Recruitment form | This telephone recruitment form will be used by study staff to recruit and track responses for potential study participants. Questions include current medical diagnoses, medication use, and participation in other Gulf War related studies. |

**Table 12. Psychiatric Diagnosis and Health Symptom Report in first 59 Participants**

| Interview Diagnosis | Frequency | Percent |
|---|---|---|
| PTSD | 12 | 7 |
| Depression | 14 | 8 |
| | | |
| Medical Conditions | | |
| Chemical Sensitivity | 3 | 5 |
| Hypertension | 18 | 31 |
| Asthma | 6 | 10 |
| Heart Attack | 2 | 3 |
| Diabetes | 2 | 3 |
| Multiple Sclerosis | 1 | 2 |
| Other Neurological Disease | 5 | 8 |
| Cancer | 6 | 10 |
| Allergies | 22 | 37 |
| Arthritis | 21 | 36 |
| | | |
| Health Symptoms | | |
| Skin Rash | 16 | 27 |
| Sleep Trouble | 36 | 61 |
| Difficulty Concentrating | 30 | 51 |
| Confusion | 16 | 27 |
| Forgetfulness | 32 | 54 |
| Joint Pain | 42 | 71 |

**Task 3a. Data entry of all questionnaires and evaluations and quality control measures will be ongoing.**

All data for the 59 completed study subjects to date have been scored, scanned into a dataset by using teleform software and cleaned through quality control measures. SPSS datasets have been created to analyze the data obtained. This procedure will be ongoing as subject recruitment progresses.

**Task 3b. Interim statistical analyses of data obtained from cognitive evaluations and questionnaire data will be performed periodically.**

Analyses of the first 32 subjects were performed and presented at the International Neuropsychological Society annual meeting in Boston, MA in February 2006. Multivariate analysis of variance was computed to compare high and low pesticide exposures on motor and attentional functioning. Chi-square analyses were computed to compare health symptom scale reporting (scale 1 = never to 5 = very often) with high and low pesticide exposure. The results are presented in table 12. Overall, the results of motor functioning analyses in pesticide-exposed veterans indicated a significant effect of high pesticide exposure and lowered mean reaction times on the continuous performance test. In addition, health symptom reporting in high pesticide exposed individuals was significantly associated with sleep difficulties and depressed mood. When clinical diagnoses and health were compared, an elevated rate of PTSD and hypertension were noted in both exposure groups. As additional subjects are recruited and statistical power is improved, regression analyses of the four grouping by regression analysis will be performed as described in the treatment of data section.

**Table 12. Preliminary Neuropsychological and health symptom Results in first 32 study participants.**

| Test | high pesticide (n = 13) mean | low pesticide (n =19) mean | Sig. |
|---|---|---|---|
| Finger Tapping (NES3) | | | |
| Dominant taps | 55.9 | 59.2 | ns |
| non-dominant taps | 52.6 | 55.3 | ns |
| dominant latency | 187.2 | 172.9 | ns |
| non-dom latency | 187.3 | 187.3 | ns |
| CPT (NES3) | | | |
| mean reaction time | 403.2 | 374.1 | .01 |
| total false positives | 2.8 | 2.1 | ns |
| total correct | 58.5 | 59.8 | ns |
| Health symptoms | | | |
| skin rash | 2.4 | 1.8 | ns |
| Fatigue | 3.5 | 2.3 | ns |
| Sleeplessness | 3.9 | 2.5 | .03 |
| difficulty concentrating | 3.5 | 2.7 | ns |
| depression | 3.1 | 2.0 | .02 |
| forgetfulness | 3.5 | 2.3 | .06 |
| confusion | 2.7 | 2.0 | ns |
| joint pain | 3.9 | 3.4 | ns |
| Diagnosis | n (%) | n (%) | |
| hypertension | 4 (31) | 7 (37) | ns |
| PTSD | 6 (46) | 4 (21) | ns |

**Task 3c. Exposure Assessment analyses for pesticides and PB will be ongoing.**

Exposure assessment analyses of individual and combined classes of pesticides will continue to be conducted during years 3 and 4 to assess dose-response relationships with health and cognitive functioning. Mr. William Bradford, lead author of the Pesticides Environmental Exposure Report, will be available to assist with these exposure estimates. Descriptive analyses for pyridostigmine bromide (PB) exposure based on total number of pills ingested as reported on the study questionnaire is presented in the table below.

**Table 13. Pyridostigmine Bromide Exposure Categories for First 59 Study Participants**

| **PB exposure** | | |
|---|---|---|
| | **Frequency** | **Percent** |
| **No** | **11** | **19** |
| **Yes** | **39** | **66** |
| **Not Sure** | **9** | **15** |
| **Total** | **59** | **100** |
| **PB Dosage** | | |
| **Total Tablets** | **N** | **Percent** |
| **0-5** | **32** | **21** |
| **6-20** | **12** | **35** |
| **21-40** | **8** | **23** |
| **41-70** | **7** | **21** |
| **Total** | **59** | **100** |

The reported range of PB dosage suggests that analyses of exposure levels will be possible when additional study subjects are recruited and higher statistical power is obtained. This will provide the ability to assess neuropsychological and health symptom reports in higher exposed individuals compared with less exposed individuals in a dose-dependent manner. This will allow for comparison of synergistic effects of high PB and pesticide exposed individuals particularly with combinations of PB and other carbamates (bendiocarb, methomyl, and propoxur) and organophosphates (azamethiphos, chlorpyrifos, diazinon, dichlorvos and malathion).

Individual pesticide exposures for the 12 pesticides of potential concern (see figure3) for the 59 recruited study participants were categorized based on questionnaire reporting and past PCI interviews. The results are presented in the table below.

**Table 14. Exposure Assessment for Pesticides of Potential Concern for First 59 Study Participants.**

| Pesticide | Not Exposed | Exposed | Percent Exposed |
|---|---|---|---|
| DEET | 36 | 23 | 39 |
| Permethrin | 46 | 13 | 22 |
| d-phenothrin | 56 | 3 | 5 |
| Azamethiphos | 34 | 25 | 42 |
| Chlorpyrifos | 44 | 15 | 25 |
| Diazinon | 44 | 15 | 25 |
| Dichlorvos | 40 | 19 | 32 |
| Malathion | 48 | 11 | 19 |
| Methomyl | 32 | 27 | 46 |
| Propoxur | 53 | 6 | 10 |
| Bendiocarb | 47 | 12 | 20 |
| Lindane | 36 | 23 | 39 |

Additional analyses comparing individual pesticides of potential concern (POPC) with cognitive and health symptom reporting will be conducted as recruitment efforts progress and adequate statistical power is obtained. However, the fact that exposure to each of the 12 POPCs was reported by the study participants indicates the feasibility of studying exposure to each of the pesticides of potential concern in our study sample.

**Task 3d. Annual reports of progress will be written.**

This report is the second annual report written for this project. The first report was submitted on February 28, 2005 and accepted on February 9, 2006.

## KEY RESEARCH ACCOMPLISHMENTS

- A pool of potential study participants was identified from a group of previously interviewed pest control personnel deployed to the Gulf War.
- Previous interviews by the Deployment Health Support Directorate (DHSD) regarding pesticide and pyridostigmine bromide (PB) exposure were obtained and used to classify these individuals into high and low exposure groups.
- Telephone interviews were performed and resulted in only a seven percent refusal rate of live calls and completion of the targeted 160 total completed exposure surveys of PCIs.
- Potential study participants were categorized based on current residence.
- Current health symptoms were identified and categorized into symptom clusters based on initial telephone interviews.
- PCIs responding to the SRBI interviews were categorized into high and low exposure groups for pesticides and PB and a pool of potential subjects have been targeted for recruitment based on residence location and exposure category.
- Fifty-nine study participants were recruited and completed the entire study protocol including cognitive evaluations, psychological interviews and exposure questionnaires. This resulted in an 84% recruitment rate for years 1 and 2.
- The first 10 study recruitment trips were greeted with interest and willingness to participate by the contacted PCIs. This is encouraging for further recruitment efforts. It appears that GW veterans continue to be interested in responding to surveys regarding health symptoms and are cooperative when asked to complete neuropsychological evaluations.
- It was determined that the study design allows for collection of all relevant data and can be accomplished in several recruitment trips throughout the country.

- Initial exposure assessments of the 12 pesticides of potential concern (POPC) and pyridostigmine bromide (PB) suggest that analyses of individual pesticides with cognitive and health functioning should be possible when the larger study sample is obtained.
- Preliminary analysis of the first 32 study participants suggested lower mean reaction times in high pesticide-exposed veterans. These positive preliminary findings are encouraging and will be further explored in the larger study sample as participants continue to be recruited.

## REPORTABLE OUTCOMES:

Publications


1. Pesticide Exposure, Health Functioning and Neuropsychological Outcome in Gulf War I Veterans (Abstract). Sullivan, K., Krengel, M., Thompson, T., Proctor, S.P. & White, R.F., International Neuropsychological Society, 34th Annual Meeting Program and Abstract Book, 2006: 208
2. Proctor SP, Gopal S, Imai A, Wolfe J, Ozonoff D, White RF. Spatial analysis of 1991 Gulf War troop locations in relationship with postwar health symptom reports using GIS techniques. Transactions in GIS 2005; 9(3): 381-396.
3. Vasterling JJ, Proctor S, Amoroso P, Kane R, Gackstetter G, Ryan M, Friedman M. Neurocognition Deployment Health Study: A prospective cohort study of Army Soldiers. Military Medicine; in press.

Manuscripts in preparation: (from previous DOD funding sources)

1. Krengel et al., Longitudinal Health Symptom Report in Treatment-seeking Gulf War-era Veterans.
2. Proctor et al., Environmental and Occupational Exposure Predictors of Multiple Chemical Sensitivity in Gulf War Veterans Assessed via a Validated Screening Instrument.
3. Sullivan et al., Neuropsychological functioning in Gulf War veterans potentially exposed to chemical weapons at Khamisiyah, Iraq.
4. Sullivan, K, Krengel, M, Proctor, S, Heeren, T, White RF. Longitudinal Cognitive Functioning in Treatment-seeking Gulf War-era Veterans.

Planned Manuscripts:

1. Sullivan et al., Cognitive Functioning in military pesticide applicators from the Gulf War.
2. Krengel et al., Health Symptom Report in pesticide applicators from the Gulf War.

Funding:

1. In June 2004, Drs. White, Krengel, Sullivan, and Proctor submitted a Merit Review grant application (Dr. White PI) to the Department of Veterans Affairs entitled "Structural Magnetic Resonance Imaging and cognitive correlates in Gulf War veterans." This study will further define neurological functioning in a previously followed cohort of treatment-seeking GW veterans and will allow for comparison of reported GW exposures with brain white matter volumes. This grant was funded and recruitment efforts have begun.

2. In April 2006, Drs. White, Krengel, Sullivan and Proctor will submit a continuing review grant application to the Department of Veterans Affairs to continue funding the Boston Environmental Hazards Center. The Boston Environmental Hazards Center (BEHC) is a science-based center within the VA Boston Healthcare System (VABHS) that is affiliated with Boston University School of Public Health (BUSPH) and School of Medicine (BUSM).

It is currently in its second of two funding phases, the first of which (1994-2000) focused on health issues in Gulf War (GW) veterans and basic studies in environmental health. The second phase (FY 2001-present) focused on advancing methodology in the field of behavioral neurotoxicology. The proposed third phase proposes to build upon the two previous funding phases by employing new methodology in behavioral neurotoxicology to study Gulf War veterans and to examine the health effects of specific neurotoxicants with cutting edge imaging techniques (structural MRI, MR Spectroscopy, and diffusion tensor imaging).

**CONCLUSIONS:**

Preliminary results of motor functioning analyses in the first 32 study participants indicated a significant effect of high pesticide exposure and lowered mean reaction times. In addition, health symptom reporting in high pesticide exposed individuals was significantly associated with sleep difficulties and depressed mood. When clinical diagnoses and health were compared, an elevated rate of PTSD and hypertension were noted in both exposure groups. Overall, these preliminary findings of motor slowing, PTSD, sleep disturbance and hypertension in this group of higher exposed pesticide control military veterans suggests that clinicians treating GW veterans should consider these domains when assessing the health and functional well-being of these aging veterans. It is possible that these preliminary results reflect residual dysfunction attributable to neurotoxicant exposure from pesticides. However, this possibility will need to be re-assessed when a larger cohort sample is obtained.

Our preliminary findings from the SRBI interviews alone suggested that GW veterans exposed to varying levels of pesticides and PB continued to report health symptoms, including high blood pressure, cardiovascular disease, skin rashes, memory problems and stress reactions. These results were confirmed when more in-depth health symptoms were ascertained from the study questionnaire with the first 59 study participants. Of interest, veterans who participated in the SRBI telephone surveys reported significantly more physical than emotional symptoms. However, when interviewed in-person several of the study participants met clinical criteria for post-traumatic stress disorder and depression. This finding stresses the importance of face-to-face interviews and evaluations with study participants in addition to postal questionnaires or telephone surveys.

It still remains of particular clinical relevance that these veterans continue to report significant physical symptoms and by documenting changes in cognitive status in conjunction with health concerns in this unique group of Gulf War veterans, the effects of exposure to neurotoxicants while in the Gulf will be further elucidated. This study will be able to confirm or dispute the conclusion of the OSAGWI health risk assessment and the RAND pesticide report which suggested that the acetylcholinesterase inhibiting pesticides including organophosphates and carbamates could be among the contributing factors to some of the undiagnosed illnesses in GW veterans by performing cognitive assessments with a group of military pesticide applicators with known chemical exposures.

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## Appendix:



more response than controls. Group differences remained after controlling for alcohol use. **Conclusions:** Despite comparable task performance, heavy marijuana using teens showed less learning-related brain response than controls, consistent with adult research. This pattern may indicate use of alternate strategies and greater rehearsal during resting blocks. Group effects were observed after 28 days of confirmed abstinence, which could suggest persisting marijuana-related changes or premorbid differences in brain functioning.

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**K. SULLIVAN, M.H. KRENGEL, T. THOMPSON & R.F. WHITE. Pesticide Exposure, Health Functioning, and Neuropsychological Outcome in Gulf War I Veterans.**

**Objective:** Current hypotheses regarding the sustained health complaints of Gulf War I (GW) veterans invoke exposure to multiple chemical exposures. In order to explore this notion, we examined veterans responsible for pesticide control for their various military units during the GW. **Participants and Methods:** GW pesticide control personnel were exposed to several different types of pesticides and at larger doses than general military personnel, making them a unique group to study. Veterans were divided into high and low exposure groups. Study participants responded to a self-report survey regarding their current health concerns, psychological functioning and cognitive complaints. They were given a comprehensive neuropsychological assessment, including measures of mood, motor functioning, short-term memory and attention. **Results:** Preliminary analyses have been completed on 33 subjects. The veterans rank health symptoms such as skin rash, fatigue, and depression as significant complaints. Multiple chemical sensitivity and hypertension appeared to be significant in this group. In addition, chronic post-traumatic stress disorder was highly prevalent. When neuropsychological variables were analyzed, veterans with high exposures were significantly different from veterans with low exposures on motor functioning and reaction time. Further analyses revealed significant effects of pyridostigmine bromide (PB)on test scores in this domain. **Conclusions:** These preliminary results suggest that there are differences in neuropsychological variables between high and low pesticide and PB exposed groups. The relationship of exposure to health outcome will be discussed.

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**M.J. TAYLOR, B.C. SCHWEINSBURG, A. GONGVATANA, O.M. AL-HASSOON, R.J. THEILMANN & I. GRANT. Microstructural Disruption of White Matter Integrity in Recently-Detoxified Alcoholics Measured with Diffusion Tensor Imaging.**

**Objective:** The goal of this study was to evaluate the impact of long-term alcoholism on the integrity of frontal and posterior cerebral white matter using diffusion tensor imaging (DTI). When axonal integrity is disrupted, an increase in diffusion and a concordant decrease in anisotropy can occur. The average diffusion coefficient (ADC) was hypothesized to be elevated in alcoholics relative to non-alcoholic controls, while fractional anisotropy (FA) was hypothesized to be lower in alcoholics. **Participants and Methods:** Thirty-three recently detoxified alcoholics (sober 2-6 weeks) in treatment at the VA San Diego Healthcare System and 16 non-alcoholic controls were evaluated using DTI. The groups were equated on age (mean = 46.5 years), education (mean = 13.3 years), gender (96% male), and ethnicity (86% Caucasian). Alcoholics met DSM-IV criteria for alcohol dependence and consumed a minimum of six drinks per day for the most recent five years. FA and ADC were calculated for regions of interest in frontal and posterior white matter. **Results:** ADC was significantly higher in alcoholics compared to controls in both frontal [$F(1,47)=4.38$, $p<.05$] and posteri
[$F(1,47)=12.08$, $p=.001$] white matter regions. In addition, signific
lower FA was present in posterior white matter of alcoholics comp
to controls [$F(1,47)=10.04$, $p<.01$] with a similar trend in frontal whi
matter. **Conclusions:** These results are consistent with studies usi
other neuroimaging methods (e.g. structural MRI and MR spectros
that suggest alcoholism-associated changes in white matter. Increa
ADC and decreased FA could indicate disorganization of cerebral wh
matter due to atrophy of both the myelin sheath and axon itself.

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**N.P. VADHAN, C.L. HART, W.G. VAN GORP, M. HANEY
R.W. FOLTIN. Does Smoked Marijuana Disrupt Decision-Mak
in Experienced Users?**

**Objective:** Recent preliminary findings from this laboratory indica
that smoking a low to moderate Δ9-THC concentration cigarette i
proved the performance of experienced marijuana users on a modifi
Gambling task. The current study is a more extensive effort to cha
terize the effects of marijuana intoxication on gambling task perfor
ance in experienced marijuana smokers. **Participants and Metho**
A within-participant double-blind design was employed in this stu
Thirty-six marijuana users, who reported smoking approximately
marijuana cigarettes per week, completed this 3-session outpatient stu
sessions were separated by at least 72-hrs. Participants complete
modified computerized gambling task once at baseline, and three ti
after smoking a single marijuana cigarette (0%, 1.8%, or 3.9%
THC). Marijuana cigarettes were administered in a double-blind fa
ion and the sequence of Δ9-THC concentration order was balanced ac
participants. **Results:** Marijuana increased the time that particip
required to complete the task, relative to placebo. However, de
making (i.e., "advantageous" vs. "disadvantageous" card selection)
money earned on the task were unaffected by marijuana. Further
of all demographic and drug use variables examined, only level of
ucation was associated with baseline performance on the modified Ga
bling task. **Conclusions:** Smoked marijuana may slow down decisi
making, but may not disrupt the advantageousness of decisions,
experienced users. These data are consistent with other findings fr
our laboratory that cognitive speed, but not accuracy, is affected by m
ijuana smoking in experienced marijuana users.

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**N.P. VADHAN, K.M. CARPENTER, C.L. HART, E.V. NUNES
R.W. FOLTIN. Attentional Bias Towards Cocaine-Related Ver
Stimuli in Cocaine-Dependent Individuals: A Comparison of Tre
ment-Seekers and Treatment-Nonseekers.**

**Objective:** When tested using modified Stroop color-naming tasks, d
dependent individuals demonstrate attentional bias as shown by in
ference from verbal stimuli associated with their drug of choice. We h
previously reported that attentional bias, measured using a Stroop co
naming task modified to include cocaine-related words, predicted tr
ment outcome. The purpose of this study was to determine the r
tionship between the treatment-seeking status of cocaine-depend
individuals and attentional bias towards cocaine-related verbal c
**Participants and Methods:** We compared performance on a drug S
task between 32 participants who were seeking treatment for their
caine dependence (25 males, seven females) and 15 participants
were not seeking treatment for their cocaine dependence (14 m
one female). **Results:** Treatment-seekers demonstrated slower reac
times in the presence of drug-related words, relative to nondrug w
(interference), whereas treatment-nonseekers demonstrated quick
action times in the presence of drug-related words, relative to non